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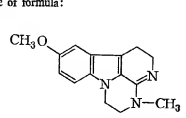
(54) PSYCHOTROPIC MEDICINAL PREPARATION

(71) We, VSESOJUZNY NAUCHNO-ISSLEDOVATELSKY KHIMIKO-FARMATSEVTICHESKY INSTITUT IMENI S. ORDZHONIKIDZE, of 7 ulitsa Zubovskaya, Moscow, Union of Soviet Socialist Republics, a Corporation organised and existing under the laws of the Union of Soviet Socialist Republics, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a psychotropic medicinal preparation for the treatment of depressions and other psychic disorders.

At present there exist a great range of psychotropic and, inter alia, antidepressant, medicinal preparations such as desipramine and imipramine. However, although these known medicinal preparations exhibit a marked therapeutic effect, they produce some side effects such as dryness in the mouth, constipation and accommodation disturbances, which limit their application for certain categories of patients.

The present invention provides a pharmaceutical preparation comprising a salt of 3 - methyl - 8 - methoxy - 3H, 1,2,5,6 - tetrahydropyrazino - (1,2,3 - ab) - beta - carboline of formula:



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where A is a pharmaceutically acceptable inorganic or organic acid, together with a pharmaceutical carrier or diluent.

The hydrochloride of the preparation according to the invention has been given a provisory name "Incazan".

The salt is an odourless white powder with a yellowish tint, has a bitter taste, is freely soluble in water, and has a molecular weight of 291.5 and a melting point of from 305 to 308°C.

The bitartrate semihydrate of this compound is prepared as slightly yellowish crystals freely soluble in water, and has a molecular weight of 339 and a melting point of from 220 to 222°C.

The pharmaceutical carrier or diluent may be liquid or solid. Thus, when it is liquid the preparation may take the form of a solution for injection comprising the active ingredient together with sterile pyrogen-free water or an injectable oil. Alternatively, where the carrier is a liquid the preparation may comprise a solution or suspension of the active ingredient in the carrier together with one or more pharmaceutical adjuncts such as antioxidants, preservatives, colouring agents, sweetening agents, and thickening agents, thus the preparation may take the form of a linctus or syrup for oral administration. Where the carrier is a solid, the preparation may take the form of, for example, a tablet, pill or lozenge or may be contained in a gelatine capsule. Alternatively, the preparation may take the form of a suppository comprising the active ingredient together with a suppository base. Also, the preparation may take the form of a pressurized composition (i.e. a so-called "aerosol" composition) comprising the active ingredient dissolved or suspended in a liquefied gaseous propellant.

In accordance with a particular embodiment of the invention, the preparation according to the invention will be present in dosage unit form (which term is intended to include containers containing fixed amounts of the active ingredient for dissolution in a sterile

solvent). These dosage unit forms will suitably contain from 10 to 150, preferably from 25 to 50, milligrams of active ingredient.

For administration per os, the preparation may be manufactured in the form of tablets, wherein the carrier is a pharmaceutical filler such as lactose, starch and calcium stearate. The amount of the active ingredient in each tablet is preferably 0.025 gm.

For parenteral administration, the recommended form comprises as the carrier a pharmaceutical solvent, for example water, for injection. In this form the amount of the active ingredient is preferably from 0.0125 to 0.025 gm per dosage unit, and the aqueous solution employed preferably has a concentration of 1.25 percent by weight.

The pharmacological properties of the hydrochloride of the preparation according to the invention and of its other salts such as bitartrate semihydrate, are the same as those of other antidepressants. The preparation according to the invention promotes the central effect of amphetamine and 5-hydroxytryptophane, and the peripheral effects of adrenaline, phenylethylamine, tyramine, serotonin and tryptamine.

The preparation according to the invention mitigates the depressing effects of reserpine and tetrabenazine as well as the cateleptic activity of phenothiazine derivatives (meterazine). As well as possessing some properties characterizing the known antidepressants such as imipramine and desipramine, the preparation according to the invention also possesses some distinctive characteristics, i.e. it produces no cholinolithic effect nor does it promote the soporific effect of Hexenal, nor the analgesic effect of Promedol nor the local-anaesthetic activity of Novocaine.

The preparation imipramine according to the invention in promoting the effects of phenylethylamine, tyramine and tryptamine. Biochemical investigations indicate that the preparation according to the invention when administered in doses sufficient to produce a marked therapeutic effect moderately inhibits monoaminoxidase activity only in the tissues of the kidneys, which indicates that its pharmacological effect is not based on antimonoaminoxidase action.

The toxicity of the active ingredient of the preparation according to the invention is quite low. Thus, the LD_{50} of the preparation administered per os to mice is 445 mgm/kg.

Toxicological investigations on the preparation according to the invention on mice, rats and rabbits using single and multiple (during one month) doses have revealed that in amounts exceeding the clinically recommended doses by 30 to 50 times the preparation has no toxic effect on the animals.

The preparation according to the invention was tested in the treatment of depressive states on 46 patients (13 men and 33 women). 33 patients were hospitalized and 13 were treated as outpatients. The age structure of the group at the time of treatment was as follows: 2 patients below 21 years of age; 20 patients from 21 to 30; 10 patients from 31 to 40; 11 patients from 41 to 50; and 3 patients above 50. By nosological forms, the patients were classified as follows:—

	subjects
1. Schizophrenia	40
including recurrent	1
shift-like	30
sluggish	9
2. Maniac-depressive psychosis	4
3. reactive depressions	2

The preparation was given in 25-mgm tablets once or twice a day (in the morning and evening). The average daily dose was from 25 mgm to 150 mgm depending on the depth and structure of a particular depression. The duration of the course was from 1 to 2 weeks to 4 months.

As a result of the treatment, depression symptoms totally disappeared in 14 patients and were mitigated in another 18 patients. The therapeutic effect was the greatest in the patients whose depressive symptoms were associated with the disturbances of the anergic pole. The preparation according to the invention also proved effective in neurotic and hypochondriac depressions as well as in shallow depressions with delirium of depressive contents.

The patients with anxious depression were given the proposed preparation in small doses, 25 to 50 mgm per day (since large doses intensified the state of anxiety) in combination with sedatives such as Triphthasine and Sonapax.

The side effects of the preparation according to the invention were as follows: agitated depression — 1 case; intensified anxiety and anxious phobics — 3 cases; dermatitis — 2 cases; headache — 1 case. It should be noted that headache and dermatitis were transitory (without the preparation being withdrawn).

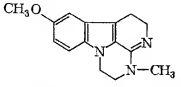
The clinical study of the preparation according to the invention leads to the conclusion that "Incazan" is an antidepressant recommendable for the treatment of sluggish, apathetic, adynamic, neurotic, hypochondriac and other depressive states.

Since it produces a few side effects, the medicinal preparation according to the invention may be recommended for the treatment of both hospitalized patients and outpatients. The preparation may be used in combination with neuroleptics, such as Triphthasine, Itaperazine and Sonapax. Itaperazine is a preparation described in the literature (see Handbook by M. D. Mashkovsky), and is 2 -

chloro - 10 - [3 - /1 - (beta - hydroxyethyl) - piperazinyl - 4) - propyl] - phenothiazine dihydrochloride. Sonapax is another phenothiazine derivative, and is also described in the abovementioned Handbook, vol. I, p. 56.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation comprising a salt of 3 - methyl - 8 - methoxy - 3H, 1,2,5,6 - tetrahydropyrazino - (1,2,3 - ab) - beta - carboline of formula:



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where A is a pharmaceutically acceptable inorganic or organic acid, together with a pharmaceutical carrier or diluent.

2. A preparation as claimed in Claim 1 in tablet form wherein the carrier is a pharmaceutical filler.

3. A preparation as claimed in Claim 2 wherein the filler is lactose, starch and calcium stearate.

4. A preparation as claimed in Claim 2 or 3 wherein there is 0.025 gm of the active ingredient in each tablet.

5. A preparation as claimed in Claim 1 wherein the carrier is a solvent for injection.

6. A preparation as claimed in Claim 5 wherein the amount of active ingredient is from 0.0125 to 0.025 gm per dosage unit.

7. A preparation as claimed in Claim 5 or 6, wherein the solvent is water.

8. A preparation as claimed in Claim 7 wherein the aqueous solution has a concentration of 1.25 percent by weight.

9. A preparation as claimed in Claim 1 in dosage unit form containing from 10 to 150 milligrams of the active ingredient.

10. A preparation as claimed in Claim 10 in dosage unit form containing from 25 to 50 milligrams of the active ingredient.

11. A pharmaceutical preparation according to Claim 1 substantially as herein described.

MARKS & CLERK,
Chartered Patent Agents,
Agents for the Applicant(s).

Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to Patent No. 1409935.

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